

REMARKS

Claims 1-35 are pending.

Claims 3, 4, 20 and 36-39 have been cancelled without prejudice.

Claims 30-35 have been withdrawn from consideration as being drawn to nonelected subject matter.

Claims 1 and 16 have been amended to recite that the polyethyleneimine (PEI) is a linear polymer. Support can be found on page 1, line 21 and page 10, lines 14-16 of the present specification. Claims 1 and 16 have also been amended to recite that the cyclodextrin (CD) is modified at no more than two positions by an activating agent to allow attachment to PEI. Support can be found in Figure 1 of the present specification which explicitly shows modification of the activating agent at two positions. It is also implicit in the description that an end group CD of the PEI-CD copolymer would have only one activating agent bonded thereto. Furthermore, claims 1 and 16 have been amended to recite that the molecular weight of PEI is less than 10,000 Daltons as was recited in claims 5 and 21, respectively. Accordingly, the present inventors were in possession of the invention as now claimed in claims 1 and 16.

Claims 5, 8 and 21 have been amended so as to clearly further limit the claims from which each depends.

The dependency of claims 5, 6, 21 and 22 has been amended so that these claims do not depend from cancelled claims.

The entire disclosure (including claims 1, 5-7, 16 and 21-23 and globally throughout the specification) has been amended to recite that the units of molecular weight for the polymers are "Daltons." It is discussed in detail below in Applicants' response to the 112, second paragraph rejection in Section [II], that there is written description support for this amendment in the specification.

No new matter has been added by way of the above-amendment.

[I] Interview

Applicants note with appreciation that Examiners Makar and Guzo granted and conducted a personal Interview with Applicants' representative, Garth M. Dahlen, Ph.D., Esq. (#43,575) on March 14, 2007 to discuss the outstanding issues. Applicants' response herein is the fruit of that discussion. The Interview is generally characterized in the March 14 Interview Summary Form, however, further details are provided below and are separated out into the issues appearing in the outstanding Office Action.

[III] Issues under 35 U.S.C. § 112 second paragraph

Claims 4-7 and 16-29 are rejected under 35 U.S.C. § 112 second paragraph for being indefinite. Applicants respectfully traverse the rejection.

In the section numbered as "5," the Examiner objects to the fact that the number average molecular weight does not have specific units in claims 4-7 and 20-23.

In response, Applicants have globally amended the specification and claims at each point where the molecular weight (MW) is described to include the units of "Daltons." As evidence of the fact that the present inventors intended for the molecular weight to be Daltons, the Examiner's attention is directed to page 10 at lines 17-25. At this portion of the specification, the specific polyethylenimine (PEI) resins of PEI2000 and PEI600 are taught to contain 46.5 and 14 units, respectively of PEI. Also, a single unit of PEI is taught to be equivalent to " $\text{CH}_2\text{CH}_2\text{NH}$ " which can be calculated to have a molecular weight of 43 Daltons. At page 6, PEI2000 and PEI600 are taught to have molecular weights of 2000 and 600, respectively. Since $2000/43=46.5$ and $600/43=14$, it is clear that the molecular weight of 2000 and 600 refers to Daltons and not kilodaltons as suggested as a possibility by the Examiner.

On a separate matter, in the section numbered as "6" of the outstanding Office Action, claim 16 is objected to by the Examiner for reciting the term "suitable conditions." In response, Applicants have amended claim 16 to delete this term.

In view of the fact that the claims, as currently amended, particularly point out and distinctly claim the subject matter which Applicants regard as the invention, withdrawal of the rejection is respectfully requested.

[IV] Issues under 35 U.S.C. § 102

The following rejections are pending:

- (A) Claims 1-9, 11-12, 16-18, 20-25 and 29 are rejected under 35 U.S.C. 102(b) as being taught by Kosak et al (US Patent Publication No: US2001/0034333); and
- (B) Claims 1-4, 8-20 and 24-29 are rejected under 35 U.S.C. 102 (e) as being anticipated by Cheng et al (US Patent Publication No: US2004/0077595).

Applicants respectfully traverse the rejections.

In order to more clearly define the invention and distinguish the invention from the cited references, Applicants have amended independent claims 1 and 16 to recite the following features:

- a) The polyethyleneimine (PEI) is a linear polymer;
- b) The cyclodextrin (CD) is modified at no more than two positions by an activating agent to allow attachment of no more than two PEI molecules attached to each CD molecule;
- c) The molecular weight of PEI is less than 10,000 Daltons.

As the MPEP directs, all the claim limitations must be taught or suggested by the prior art to establish a *prima facie* case of anticipation. See MPEP § 2131. It is Applicants' position that neither Kosak nor Cheng teach or fairly suggest all of the claim limitations, of the claims as currently amended. Details of Applicants' position are provided below.

Kosak's Disclosure:

Kosak teaches that CD molecules are covalently linked through a linkage to form a polymer of CD molecules. As noted in claim 14 of Kosak, the linkages are disulfide linkages,

protected disulfide linkages, ester bonds, aldehyde bonds, amide bonds, polypeptide bonds and hydrazone linkages. Thus, Kosak teaches polymerized CD without intervening PEI units. Kosak does not describe a linear copolymer of units comprising CD linked to PEI, as is required by instant claims 1 and 16.

Kosak's patent does mention PEI, but only for use as a crosslinking agent to crosslink an amino-containing cationic substance (PEI800) with the thiolated CD dimers, trimers and polymers. As the CD polymers are synthesized before interacting with PEI, PEIs are linked as side chains to the CD polymers.

Furthermore, Kosak fails to teach or suggest that the PEI-CD copolymer can be used for gene delivery either *in vitro* or *in vivo* as in the present invention.

Instant Application:

The instant biodegradable copolymers are prepared in such a way that the CD molecules are covalently linked through low MW PEI to form a CD-PEI copolymer wherein the CD molecules and the PEI molecules make up the copolymer backbone.

Low MW PEIs or CD molecules have a higher MW than the spacers Kosak used and, as such, are not biocleavable, i.e., they are much more stable and are best described as being biodegradable.

Most importantly, because of the design, the backbone of the instant copolymers contains two monomer units: low MW PEI and CD. The present inventors have created a way to control the reaction conditions to make CD interact with only two PEI molecules giving the so called AB block copolymers.

Kosak's:

CD polymer

CD polymer + PEI

Or

CD polymer + PEI

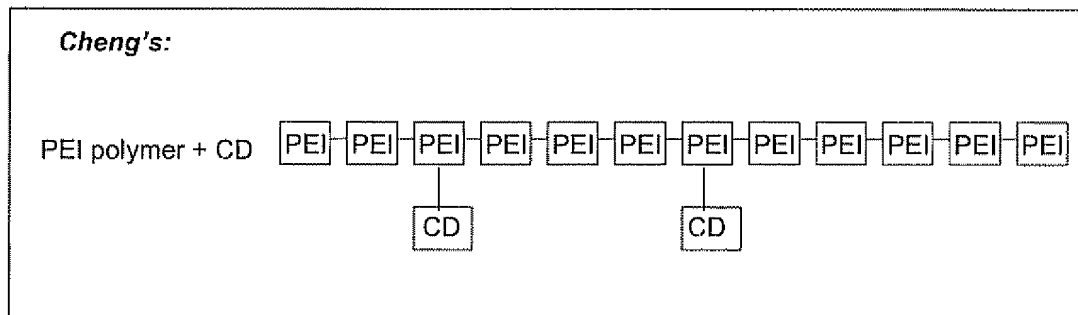
Our polymer:

Equal amounts of PEI and CD in a polymer, more stable, can be used for in vitro and in vivo DNA delivery

Cheng:

DRN/GMD/mua

In formula II of Cheng, CD is linked to a polymer with a monomer P. This structure is clearly different from the instant copolymer. If PEI25kDa is understood as a polymer made from many low MW PEI, then Cheng's polymer has a structure as follows:



Furthermore, Cheng is almost completely silent with respect to the molecular weight of the PEI molecules. Apparently, the only description of the molecular weight of Cheng is in Example 35 which uses PEI25000. In order to further distinguish the present invention from Cheng, claims 1 and 16 have been amended to recite that the molecular weight of the PEI is less than 10,000 Daltons.

It was Applicants who surprisingly found that the molecular weight of the PEI molecules in the PEI-CD copolymers has a strong affect on the toxicity of the copolymer. The present specification teaches that the PEI600 and PEI2000 has low toxicity whereas PEI25000 (such as the one used by Cheng in Example 35) is highly toxic in the cell viability test on page 11 of the present specification.

Accordingly, the instantly claimed PEI-CD copolymers are structurally distinct from the polymers of Cheng and this structural distinction also leads to advantageous properties which would not be expected based on the description of Cheng.

In conclusion, Kosak and Cheng teach polymers which are structurally different from the instantly claimed copolymer. While Cheng's polymers use PEI as the backbone of the polymers and Kosak's polymers use CD as the backbone, the backbone of the instant copolymers contain

essentially equal amounts of PEI and CD and are linked in a way to use two units alternatively. In addition, the instant application is the first to teach how to use these copolymers to deliver DNA *in vitro* and *in vivo*.

Based on the foregoing, a *prima facie* case of anticipation cannot be said to exist, and withdrawal of the rejections is respectfully requested.

Information Disclosure Statement

Applicants note from the signed PTO-1449 form which was originally filed as part of the Information Disclosure Statement (IDS) on April 23, 2004 (which is attached to the outstanding Office Action), that the Examiner has drawn a line through the reference to Godbey et al. The Examiner has indicated that Applicants did not include a copy of Godbey et al. with the April 23, 2004 IDS. However, according to Applicants' records, a copy of Godbey et al. was provided for the Examiner. Accordingly, Applicants enclose herewith a new copy of Godbey et al and evidence (stamped postcard receipt) that this reference was enclosed with the April 23, 2004 IDS. Furthermore, Applicants enclose a new PTO/SB08 form which lists Godbey et al. The Examiner is requested to initial and sign the enclosed PTO/SB08 form and return the signed form to Applicants in the next communication so that it is clear on the record that Godbey et al. has been considered.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Garth M. Dahlen, Ph.D., Esq. Reg. No. 43,575 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: March 21, 2007

Respectfully submitted,

By 

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Attachments: 1) Godbey et al.

2) stamped postcard receipt showing that Godbey et al. was enclosed with the April 23, 2004 IDS

3) new PTO/SB08 form which lists Godbey et al.

